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Pattern of HIV-1 drug resistance mutations among patients failing thymidine analogue and non-thymidine analogue based first-line failure in South India

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Background: HIV-1 Drug Resistance Mutations (DRMs) among individuals with Immunological failure (IF) on different NRTI based first-line regimen, Thymidine analogue (TA) - AZT & D4T and Non-Thymidine Analogue (NTA) -TDF; and predict viral drug sucessibility to gain vision about optimal treatment strategies for second-line.

Methods & Materials: Cross-sectionaly, 400 HIV-1 infected patients, failing first-line HAART were included in the analysis. HIV-1 pol gene spanning 20 – 240 codons of Reverse Transcriptase was genotyped by validated homebrew method and mutation pattern was examined, (IAS-USA 2014 and Stanford HIV drug resistance database v7.0)

Results: Out of 400, majority had subtype C infection 97.2% (n = 389) and any DRM was seen in n = 379. On analyzing two groups, duration of failure was longer for TA (n = 279), with the median of 57.6 (IQR 35.2-76.2) months compared to NTA (n = 121), 24 (IQR 11.2-51.8) months, ($p < 0.05$). Among individual mutation analyzed K65R (23.2% vs. 4.6%), L74V (10.7% vs. 0.3%) and Y115F (11.6% vs. 0.7%) was significantly higher among NTA compared to TA, ($p < 0.001$); whereas M184V and TAM accumulation was significantly high in TA ($p < 0.05$), Among NNRTI mutation K101E/P/H (18.1% vs. 8.5%), G190A (32.7% vs. 27.6%) was higher among NVP ($p < 0.05$) and K103N (57% vs. 35.1%), V106M (30.2% vs. 12.1%) was higher among EFV ($p < 0.05$).

Based on the mutation pattern observed in both groups, we analyzed the impact of DRMs on future therapy and found as; in TA high level of resistance was observed to all drugs, except TDF (71.5%) >AZT (56.3%) >ABC (50%). In the same way among NTA AZT (78.6%) >TDF (63.7%) and >ABC (38.1%) was observed. On combining both, among TA failures still 56.7% and 71.4% can be considered for AZT and TDF based second-line. Similarly, among NTA failures still 63.7% and 78.6% can be considered for TDF and AZT based second-line regimen.

Conclusion: As expected TA based first-line failure had developed more cross resistance compared to NTA group, but still majority can be recycled in the same regimen as second-line option. Further, in resource limited settings, treatment outcome is monitored immunologically; when virological based treatment monitoring comes in practice further emergence of DRMs can be avoided by early switching.

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The impact of HIV infection on the burden and severity of influenza illness in Malawian adults

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Background: The impact of HIV infection on the incidence and severity of influenza illness in adults in sub-Saharan Africa (SSA) is unclear. Although annual seasonal influenza vaccination is recommended for HIV-infected persons in developed settings, it is not part of routine HIV care in SSA.

Methods & Materials: At the Queen Elizabeth Central Hospital in Blantyre, Malawi, we conducted: i) a prospective cohort study, to compare the incidence of influenza illness between HIV-infected and HIV-uninfected adults; ii) a case control study, to determine risk factors for severe influenza presentation. Cases were adults with severe influenza illness (lower respiratory tract infection (LRTI) requiring hospitalization). Controls were adults with mild influenza presentation (influenza-like illness (ILI) managed as outpatients). Influenza was identified from nasopharyngeal specimens by real-time reverse transcription polymerase chain reactions (RT-PCR).

Results: The cohort study enrolled 360 HIV-infected (median CD4 count 390 cells/cm^3) and 248 HIV-uninfected adults, providing 520 and 348 person-years of observation, respectively. Between April 2013 and March 2015, 24/229 (10.5%) ILI episodes in HIV-infected and 5/119 (4.2%) in HIV-uninfected adults were influenza PCR-positive. HIV-infected adults had almost three times increased risk of laboratory-confirmed influenza illness compared to HIV-uninfected adults (incidence rates 46.0 vs. 14.5 per 1000 person-years; incidence rate ratio 2.75, 95% confidence interval (CI) 1.02-7.44). In the case control study, 56/518 (10.8%) patients with hospitalised LRTI, and 88/642 (13.7%) with ILI were influenza PCR-positive. HIV prevalence among the influenza-positive cases and controls were 70% and 30% respectively. On multivariable analysis, HIV infection was the most important risk factor for severe influenza presentations (odds ratio (OR) 4.98, 95%CI 2.09-11.88),

with a population attributable fraction (PAF) of 57%. Unimproved sanitation (OR 3.14, 95%CI 1.25-7.84) and food insecurity (OR 20.85, 95% CI 1.97-221.16) were also associated with hospitalised influenza.

Conclusion: A substantial burden of influenza was identified in both HIV-infected and uninfected Malawian adults. Moreover, HIV-infected adults appear to have increased susceptibility and severity of influenza presentations. Influenza vaccination in this at-risk group is likely to be beneficial. However, the optimal mechanism for vaccine introduction and evaluation in already overstretched health systems in SSA will need to be determined.

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Attenuated resting memory B cell compartment in HIV infected children despite Highly Active Antiretroviral Therapy (HAART)

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Background: Studies assessing the impact of Highly Active Antiretroviral Therapy (HAART) on B cell subpopulations in HIV infected children are scarce. Hence, we undertook this study to describe the B cell compartment and the effect of HAART in a cohort of HIV-infected children (<5 years of age).

Methods & Materials: Treatment-naïve HIV infected children were enrolled and followed regularly till 12 months; HIV uninfected children with no major illness were recruited as healthy controls (n = 51). CD10-CD20+ B cells were characterized as naïve (CD21+CD27-), resting memory (21+CD27+), activated memory (CD21-CD27+) and tissue like memory (CD21-CD27-) B cells. The frequency of these B cell subpopulations was evaluated in HIV-1 infected children at baseline, 6 months and 12 months of HAART. The percentage of B cell subpopulations at baseline were compared between HIV infected and uninfected children.

Results: Twenty-seven HIV-1 infected HAART naïve children of median age 22 (12-44) months [boys: 63%] were enrolled. At baseline, Marked differences were observed in B cell subpopulation distribution among HIV infected children and healthy controls. The median frequencies of naïve B cells and resting memory B cells were significantly lower ($p = 0.001$; $p = 0.0005$ respectively), while activated memory and tissue like memory B cell pool were significantly expanded in HIV infected children compared to healthy controls ($p < 0.0001$ for both). At 12 months of HAART, no significant differences were observed in the frequencies of naive ($p = 0.88$) and activated memory ($p = 0.13$) B cells between HIV infected HAART treated children and healthy controls. However, the frequency of tissue like memory B cells was still significantly higher in HIV infected HAART treated children ($p = 0.001$) and significantly inferior resting memory B cell pool was observed compared to their healthy counterparts ($p = 0.002$).

Conclusion: This study re-iterates the effectiveness of HAART in pediatric population; however, it raises concern about the inadequate reconstitution of B cell compartment at 12 months of treatment.

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Evaluation of novel rapid bead based method for capturing of Mycobacterium tuberculosis in sputum

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Background: Tuberculosis is one of the major global health problems. The diagnosis of TB relies primarily on the identification of acid fast bacilli (AFB) by microscopy. Microscopic examination of direct specimen smear stained with Ziehl-Neelsen (ZN) staining and studies have found this assay to be less sensitive. TB-Beads can be used as an alternative to centrifugation for concentration of TB bacilli. The current study intends to compare the conventional specimen pre-treatment with the novel technique of sample pre-treatment based on magnetic beads in single tube.

Methods & Materials: We evaluated the feasibility of a ligand-coated magnetic bead technology to concentrate *M. tuberculosis* in single tube (decontamination, concentration and staining) prior to detection by LED-based fluorescence microscopy. We compared the quality of this method with the Ziehl-Neelsen (ZN) microscopy performed after modified Petroff (MP) method and direct fluorescence microscopy (FM) in sputum samples at a reference laboratory in India. The kappa coefficient (K^c) analysis performed for positive correlation between the tests and LJ culture taken as a gold standard for evaluation to sensitivity and specificity of performed tests.

Results: The head to head comparison on all performed tests were performed, concentrated magnetic bead-FM possess higher positivity rate (58.7%) than and direct microscopy (45.3%) and MP-ZN microscopy (41%) among all 150 sputum samples. By comparing with culture the concentrated magnetic bead-FM (88.5%) had significantly higher sensitivity than MP-ZN (73%) and direct FM (74.4%). The specificities of magnetic bead FM direct FM and MP-ZN microscopy were 74%, 86% and 94% respectively. The fair correlation found between culture and ZN microscopy ($K^c = 0.67$), magnetic bead-FM ($K^c = 0.62$) and $K^c = 0.60$ with direct FM.

Conclusion: Newer Magnetic bead concentration of Mycobacteria in clinical samples showed a significant improvement in the sensitivity of microscopy compared to direct FM and concentrated ZN microscopy. These methods will be improving the diagnostic performance of smear microscopy and reducing the tuberculosis burden by single tube processing.

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